Acute Adrenal failure; a potentially fatal consequence of an adulterated herbal remedy

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Running Title

HPA suppression and herbal remedy

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HS researched the literature and wrote the first draft. HNB made the diagnosis and is responsible for the clinical care of the patient. LTF analysed the tablet. RG co-ordinated analyses and helped research the literature. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Abstract

Herbal remedies adulterated with glucocorticoids can cause Cushing's syndrome. We report a more sinister presentation of an "herbal remedy" adulterated with glucocorticoids; causing a potentially fatal acute adrenal failure precipitated by acute illness. Investigations were consistent with adrenal suppression and confirmed, by tablet analysis, to be due to an "herbal remedy" adulterated with synthetic betamethasone/dexamethasone. This case highlights the need for clinical vigilance and patient education about the potential risks associated with the use of unlicensed treatments and the role of tablet analysis in routine biochemistry.

Introduction

The worldwide use of complementary and alternative medicines is increasing and herbal medicines are often used as a primary health care source [1,2]. Complementary and alternative medicines are often considered safe [1] but there have been concerns regarding the safety and efficacy of such treatments [1-3]. Cushing's syndrome is commonly caused by prescribed glucocorticoids [4-7]. With one possible exception [5], Cushing's syndrome is not caused by herbal remedies other than those adulterated with glucocorticoids [6-12]. This commonly presents with Cushing's syndrome [5-7, 11, 12] but may also present with adrenal suppression [8].

We report a more sinister presentation of an "herbal remedy" adulterated with glucocorticoids, subsequently causing a potentially fatal acute adrenal failure precipitated by acute illness, due to unrecognised glucocorticoid-induced adrenal suppression.

Case Report

A 61 year old woman, of Pakistani origin, was admitted to the Intensive Care Unit (ICU) with pneumonia and acute kidney injury (AKI). Admission comorbidities and current treatment included obesity, type 2 diabetes (Metformin), hypertension (Bisoprolol), hypercholesterolaemia (Atorvastatin), osteoarthritis of the hips (Paracetamol), fibromyalgia, primary hypothyroidism (Levothyroxine), chronic back pain (Gabapentin) and previous cholecystectomy. As she was persistently hypotensive, she underwent a standard short synacthen test which was consistent with adrenocortical insufficiency (Table) and was initiated on hydrocortisone therapy. She made a good recovery in response to steroids and antibiotics. She was discharged on her pre-admission medication together with hydrocortisone 10mg in the morning, 5mg in the afternoon, and 5mg in the evening with arrangements to be reviewed in the endocrinology clinic. In the

interim, she sustained and was conservatively treated for a traumatic right 5thmetatarsal fracture.

During her outpatient endocrine follow up, a repeat failed short synacthen test confirmed adrenal failure and the cause of the adrenal failure was investigated. There was no personal or family history of tuberculosis and her ICU CT thorax showed no evidence of pulmonary TB or adrenal calcification. Although not Cushingoid, the combination of diabetes, obesity, recent foot fracture and undetectable 9am serum cortisol raised the possibility of exogenous steroids. However, prior to her ICU admission she had never taken or been prescribed any oral, inhaled, intra-articular or cutaneous steroids. On further specific questioning about herbal remedies and over the counter medications, she readily informed that, for over four years, she had been taking a herbal remedy (QURS SAFFRON). This was supplied by a non-medical practitioner in Pakistan for chronic joint pain with excellent therapeutic effect. The listed ingredients in QURS SAFFRON are "meadow saffron, colchicum, murdannia, asparagus, pellittory, china root, mace, dill, mint peppermint, fennel fruit, horse radesh, kala dana, black pepper, long pepper, saffron and coral." As none of these, to our knowledge, has glucocorticoid activity we requested tablet analysis which, using ultra-performance liquid chromatography-time of flight-mass spectrometry, detected betamethasone/dexamethasone and indomethacin. The patient was advised to stop taking the herbal remedy and her hydrocortisone regime was continued. Her chronic joint pain recurred. The results of investigations were consistent with adrenal suppression from exogenous steroids [Table]. She continues to be weaned off the hydrocortisone depending on Hypothalamic-Pituitary-Adrenal axis recovery.

Table: Results of relevant investigations

Test	ITU	On recovery following discharge	Normal values
Synacthen Test 0 minute cortisol (nmol/L) 30 minute cortisol (nmol/L) 60 minute cortisol (nmol/L)	 276 292 -	 <22 43 54	 >450 nmol/L at 30 mins
Baseline ACTH (ng/L)		<5	0 - 46
Herbal Tablet Analysis		Betamethasone/Dexamethasone Indomethacin	

Discussion:

Adrenal failure, if unrecognised, may be fatal particularly in acutely ill patients [13]. An inadequate cortisol response to synacthen is often the diagnostic test of choice in defining adrenal failure [14]. Although a low serum cortisol (usually defined <100nmol), particularly during illness, is suggestive [7, 14]. A low threshold for adrenal failure should be maintained in those with any of the following features: volume depletion, hypotension, hyponatremia, hyperkalaemia, fever, abdominal pain or hyperpigmentation [6, 14-15]. In this case persistent hypotension was the indication for the synacthen test.

Serum cortisol must be interpreted in the context of acute illness. Cortisol circulates as biologically active free cortisol (<5%) but mostly as biologically inactive cortisol bound to the carrier proteins cortisol binding globulin (CBG) and albumin [4, 15]. Serum cortisol is a measurement of both free and bound cortisol. Although usually elevated in acute illness, serum (total) cortisol may also be misleadingly low as it does not accurately reflect serum free cortisol, since CBG and albumin are negative acute phase reactants and therefore total serum cortisol may be reduced in ill patients [15]. A suboptimal serum cortisol response to synacthen during acute illness should therefore be confirmed in the recovery period as was in this case.

Having confirmed adrenal failure, the underlying cause needs to be determined. Apart from a history of autoimmune primary hypothyroidism there was little to support autoimmune adrenalitis and none for TB adrenalitis or hypothalamic-pituitary disease. The undetectable ACTH excluded primary adrenal failure. The patient's undetectable serum cortisol and ACTH and co-morbidity made adrenal suppression most likely but there was no apparent history of exogeneous steroid usage and only specific questioning uncovered use of an herbal remedy. As the listed ingredients of the herbal remedy (Qurs Saffron) did not contain glucocorticoids, tablet analysis was essential to make the diagnosis of adrenal suppression from glucocorticoids adulterating an "herbal remedy".

This case report illustrates the huge risk to patients who use "herbal remedies" especially those who are unaware or misled about their contents. In this case, the steroid-adulterated herbal remedy may have caused or contributed to her diabetes, weight gain, pneumonia and foot fracture. Additionally, the sudden cessation and subsequent inability to mount a cortisol response during illness resulted in a potentially fatal acute adrenal failure. Ironically the "herbal remedy" had an excellent therapeutic effect and its withdrawal caused a relapse of the patient's chronic joint pain.

The use of alternative medicines is expanding exponentially and is estimated to be generating an annual worldwide market nearing 60 billion US dollars. [16]. Herbal medicines are used worldwide to treat a variety of medical conditions and mostly cause no ill-effect [1, 16-18]. Case reports, however, have highlighted herbal remedies causing toxicity and poisoning due to contamination with other plant materials, heavy metals and micro-organisms [2, 3]. Concerns, therefore, have been raised regarding the efficacy, safety and monitoring of the manufacture of herbal remedies [1,3,19] and their frank adulteration [6-12]. Furthermore, potential herb-drug interactions should be considered in prescribing conventional medications. [3, 20-23]

In summary, we report a potentially fatal adrenal failure as a result of adrenal suppression due to an "herbal remedy" adulterated with potent steroids (and NSAIDs) and the crucial role of tablet analysis in confirming the diagnosis. We suggest that in clinical consultations, specific enquiries are made regarding the use of herbal remedies and alternative medicines. As well as maintaining a high index of clinical suspicion that these, particularly unregulated concoctions, may cause comorbidity. This report illustrates not only the harm of taking unregulated medication but also the unrecognised potential harm of their acute withdrawal. Ultimately, this case highlights the need for clinical vigilance and patient education about the potential risks associated with the use of unlicensed treatments.

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